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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/816,304	ROTHSCHILD ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,19-37 and 40* is/are pending in the application.

4a) Of the above claim(s) *25-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,19-24 and 29-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This application is a continuation of 09/538165. The status identifiers in the preliminary amendment are relative to the most recently pending claims in the parent application. The remarks filed with this application refer to the rejections that were pending in the parent application at the time of filing the instant application. These rejections have been applied but modified to provide further explanation. The claims which were withdrawn due to the restriction set forth in the parent application (see office action mailed 5/8/01) are indicated as withdrawn in this application consistent with the prosecution in the parent application. Thus, in this application, claims 1, 4-10, 19-37 and 40 are pending. Claims 25-28 are withdrawn from consideration. Claims 1, 4-10, 19-24, 29-37, and 40 are examined on the merits in this office action. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Applicant's remarks are addressed after a statement of all rejections. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Specification

2. The description of the drawings is not complete because it does not refer to all of the different drawings. For example, the drawings include Fig. 1 as well as Fig. 1A, yet the description of the drawings refers to only "Figure 1." This is likewise true for Fig. 2A, 2B, 2C, 3A, 3B, and 4D.

3. The specification provides three tables one on each of pages 15, 23, and 25. These tables are not numbered consecutively since there are two tables numbered "Table 1" and one table numbered "Table 2." Correction is required. Applicant is advised upon correction to review the

specification to ensure that the text of the specification refers to the tables using the amended numbering system.

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s):

The sequences identified in the specification do not always match with the sequences in the CRF or the paper copy of the sequence listing. For example, the specification at **page 10**, line 15 provides the sequence of a "forward primer"- 5'TGG CAA TAG CCA AGA ACA AG-3' and identifies this sequence as SEQ ID NO: 6. However, this sequence is provided as **SEQ ID NO: 5** in the sequence listing. This problem continues with the sequences recited in lines 16, 18, and 19 of **page 15**. Likewise, this problem occurs at lines 21 and 22 of **page 13** and lines 9-11 and 32-34 of **page 18**. Line 24 of **page 19** refers to primers having SEQ ID NO: 10 and 11, however SEQ ID NO: 11 is not a primer, it is an amino acid sequence. This problem also occurs in the FIGURES as described in the brief description of the drawings on pages 6 and 7, applicant should review the reference to SEQ ID NO: 3 in figure 2, SEQ ID NO: 4 and SEQ ID NO: 5 in figure 3 and the additional recitations of sequences.

The drawings include a number of sequences that are not identified with proper sequence identifiers which may be present in either the drawing itself or the brief description of the drawing. For example, 5 depicts two amino acid sequences and two nucleotide sequences, yet the description of the drawing refers to only one SEQ ID NO. Four different SEQ ID NO should be listed in describing this figure, or within the figure itself. Likewise, figure 6 refers to a wide

variety of different polypeptide sequences and none of these are identified with proper sequence identifiers.

In order to comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825), Applicant must submit, as necessary, a new CRF and paper copy of the Sequence Listing containing these sequences, in addition to the previously listed sequences, an amendment directing the entry of the Sequence Listing into the specification, an amendment directing the insertion of the SEQ ID NOs into the appropriate pages of the specification and a letter stating that the content of the paper and computer readable copies are the same.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 35, and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitations of "selecting animals which possess a desired MC4R genotype indicative of a significantly associated phenotypic trait" in claim 33, "correlated with a phenotypic trait" in claim 35 and "said polymorphism being one which is

associated with a phenotypic trait" in claim 37 appear to represent new matter. These amendments each broaden the claims in question so as to encompass the screening for or selection of animals that have ANY phenotype. The instant specification does not contain disclosure that indicates the contemplation of such claims, indeed, the specification discusses only the relationship between the polymorphism in the MC4R gene and meat quality traits. No specific basis for these limitations was identified in applicant's paper, nor did a review of the specification by the examiner find any basis for the limitations.

Since no basis has been identified, the claims are rejected as incorporating new matter.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 4-10, 19, 22, and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, it is not clear what it means for a an amino acid position to be "analogous to amino acid 298 of a human MC4R gene product." How are the positions "analogous?" do they both have to have an asparagine codon? What required context surrounding a particular position is necessary to identify a particular position as analogous to the human amino acid at position 298? The metes and bounds of what is being claimed is unclear. Further, if one is looking at the DNA of a single animal, how can one identify if there has been a "change from an aspartic acid codon to an asparagine codon" in the single individual? It would be clearer to recite that a particular codon is present, not that a change is identified. All claims which depend from claim 1 are indefinite over these same recitations.

Claim 19 is indefinite, because while the instant specification discloses a TaqI polymorphic site present at position 678 of instant SEQ ID NO: 1, this polymorphic site does not appear that it would be present at position 678 of the DNA amplified using instant SEQ ID NO: 5 and SEQ ID NO: 6. Comparing these primers to instant SEQ ID NO: 1, one can note that instant SEQ ID NO: 1 overlaps with the primer identified in the sequence listing as SEQ ID NO: 5 by only the final five nucleotides of SEQ ID NO: 5. This means that when SEQ ID NO: 5 is used to amplify a portion of the MC4R gene from pigs the polymorphic position referred to by the instant invention would not be present at position 678 in particular, but would be present at a later numbered position if one begins with position 1 being at the beginning of the amplified fragment when SEQ ID NO: 5 is used as a primer. Therefore, it is confusing if applicant intends to refer, in claim 19 to a different polymorphic site than is the subject of most of the discussion of the instant specification, or if the numbering convention used in the claim is wrong in light of the fact that a primer having SEQ ID NO: 5 would amplify a fragment that has 15 nucleotides upstream of the fragment depicted in instant SEQ ID NO: 1. Review and clarification of the claim is required.

Claim 22 refers to a nucleotide that is present at "base 678 of the MC4R gene" and this is indefinite because the number of a nucleotide present at a particular position is entirely dependent on the primers used to amplify the fragment. There is no known "base 678 of the MC4R gene" for all pigs or for all possible MC4R genes. For pigs in particular, the full length coding sequence of the MC4R gene is not disclosed in the specification, so what "the MC4R gene" refers to itself is indefinite. Even still, the number of a position in the gene is entirely

arbitrary depending on where one begins counting (in the promoter, at the start ATG, at the beginning of an amplification fragment, etc). Claim 22 is further indefinite for this reason.

Claim 23 is further confusing because it depends from claim 22 which requires the identification of a particular restriction fragment pattern, yet claim 23 requires the identification of different patterns as representative of allele 1 and allele 2 of the MC4R gene. Thus, claim 23 appears to conflict with claim 22 from which it depends.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-10, 19-24, 29-37, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for identifying a pig which possesses a genotype indicative increased pH, decreased Minolta, decreased drip loss, or increased rate of weight gain, wherein a pig homozygous for adenine at position 678 of SEQ ID NO: 1 is indicative of said pig being more likely to have the phenotype than a pig with a guanine at position 678 of SEQ ID NO: 1, said method comprising detecting the nucleotide present at position 678 of SEQ ID NO: 1, and relating the nucleotide to the phenotype, does not reasonably provide enablement for methods which screen other species of animals, or methods which utilize drawn conclusions based on nucleotide(s) present at positions other than 678 of SEQ ID NO: 1, or methods which identify pigs that would produce meat with any other relative meat qualities or methods which identify/screen for any animal having any possible phenotypic trait, particularly, the specification is not enabling for the detection of pigs that would produce meat with

differential marbling based on the nucleotide present at position 678 of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Each of the rejected claims are broadly drawn to include at least one of the following: methods for screening any animal, methods for using any polymorphism in the MC4R gene, methods for using polymorphisms which are "linked" to the instantly disclosed polymorphism or methods for identifying animals that would produce meat with marbling qualities or other meat qualities unidentified in the claims or the specification, or methods which identify animals that have any possible phenotype associated with polymorphism in the MC4R gene.

The specification teaches the use of primers (instant SEQ ID NO: 5 and SEQ ID NO: 6, as identified in the sequence listing) to amplify a portion of the porcine MC4R gene, and that the product size from the PCR is approximately 750 nucleotides (p. 13-14). Subsequent to digestion with the restriction enzyme TaqI, applicant reports the identification of two alleles: allele 1 having bands of about 466, 225, and 76 nucleotides and allele 2 having bands of 542 and 225 base pairs (p. 14). The specification teaches that the polymorphism results from a G→A transition at position 678 of SEQ ID NO: 1, and that the polymorphism results in a missense mutation in the encoded porcine polypeptide from aspartic acid codon to asparagines codon at position 298 of the MC4R protein (p. 15, 1st paragraph). Instant SEQ ID NO: 1 does not appear to be a full length coding sequence for the MC4R receptor since it does not contain the full sequence that would align with the human receptor (see Figures 2 and 3).

The specification makes reference to three markers which are significantly linked to the disclosed porcine polymorphism, markers referred to as SO331, BHT0433, and SO313 (p. 15-

16). The specification does not, however provide any discussion of the structure of these markers, which alleles are indicative of what trait, or how to use these particular markers in the claimed assay. MPEP 608.01 (p)[R-2] teaches that "While the prior art setting may be mentioned in general terms, the essential novelty, the essence of the invention, must be described in such details, including proportions and techniques, where necessary, as to enable those persons skilled in the art to make and utilize the invention." For claims which rely on "linked markers" and specifically claim 31 which mentions these markers in particular, the guidance in the specification is not sufficient to use these markers in any assay for detection of traits in pigs, or any other animals. Furthermore, claim 31 is generic to detection in any animal, and these markers appear to be specific and particular markers identified within the pig genome (based on applicant's limited discussion of them) and there is absolutely no guidance as to how these particular markers could be used in other species of animals, like cows or chickens or sheep, all of which are encompassed within the claims.

The specification further provide data which demonstrate that pigs homozygous for adenine at position 678 of SEQ ID NO: 1, on average, produce meat that has increased pH, decreased Minolta, decreased drip loss, or increased rate of weight gain relative to pigs with a guanine at that position (see Table 2, page 23). Based on these data, it is reasonable to conclude, for pigs, that the identification of the nucleotide present at this position in the porcine gene is indicative these traits.

No significant association is demonstrated between the presence of the polymorphism and marbling in meat from pigs (see Table 2, page 23). Thus, claims which specifically recite that the polymorphism is indicative of a favorable meat quality, specifically having favorable

marbling are not supported by the findings provided in the instant specification (for example, independent claim 20). Furthermore, based on the data presented in the instant specification it is highly unpredictable as to whether this specific trait is in fact associated with the presence of the polymorphism. The prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion. Because applicant's attempt to associate the disclosed polymorphism in pigs with the trait of marbling resulted in a p value of 0.42, it is not possible to conclude that a reliable association exists between marbling and the presence of a particular allele at the identified polymorphic site.

The prior art teaches the unpredictability of using nucleic acid sequence analysis for the determination of a phenotype. For example, Hacker et al (1997) teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (pages 623-627). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample

sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph).

The prior art demonstrates that this mutation is associated with animal fat content, growth rate and feed consumption (WO 00/06777). The prior art is silent with respect to other possible polymorphisms in the MC4R gene or with respect to the association of this particular polymorphism with favorable meat qualities in any other meat producing animal. Neither the specification nor the prior art provide evidence of any universal correlation between MC4R and meat quality in all animals which would conclusively associate the polymorphism instantly disclosed with favorable meat quality in any other animal. Furthermore, the prior art does not provide any evidence that this particular polymorphism is associated with all measures of meat quality.

With regard to the claims that are broadly drawn to testing any animal for any phenotype associated with polymorphism in the MC4R gene, the art supports the fact that it is highly unpredictable which polymorphisms within the MC4R gene will be associated with which phenotypes. For example, Gotoda *et al.* were unable to establish a relationship between a polymorphism in the human MC4R gene and any phenotype (Diabetologica, 1007). Furthermore, the neither the prior art nor the instant specification provide even the sequence of the MC4R protein or nucleic acid encoding the protein for any other traditional "meat" producing species of animal (such as cows, sheep, chicken, fish, etc.).

The art is highly unpredictable with regard to the presence and functionality of polymorphic sites in genomic DNA. First, it is unpredictable whether any additional polymorphisms exist in the porcine MC4R gene, or whether the instantly disclosed

polymorphism is present in the genomes of other animals. Genetic polymorphisms are the elements which render individuals unique, but many genes are highly conserved and do not yield polymorphisms between individuals of a single species. Some genes even lack polymorphisms between members of different species. The specification and prior art provide no guidance as to whether any other polymorphisms exist, or whether the instantly disclosed polymorphism is present in the genomes of other animals besides pigs. For practice of the claimed invention even within pigs, this is further complicated by the fact that the instant specification provides only a partial sequence of the porcine MC4R gene. Second, after a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with favorable meat quality. Thus, the claimed method of screening animals, for enablement of the full scope, requires the use of unpredictable and potentially non-existent products, and further associations between these products and phenotypes. In this case, the genus is itself undefined and undue experimentation is required to identify which polymorphisms, none of which are known other than the disclosed example, have the utility of being associated with favorable meat quality.

Furthermore, it is entirely unpredictable whether or not the MC4R genes of any other organisms contain a SNP at a position homologous to that described in the instant specification for the porcine MC4R gene, whether such a polymorphism would effect a TaqI site, and whether or not such a polymorphism would be indicative of any phenotypic traits. The unpredictability of the interspecies conservation of polymorphic sites is demonstrated in the prior art of Mummidi et al (2000). Mummidi et al teaches the sequence analysis of the CC chemokine receptor 5 (CCR5) gene in humans and non-primates. Notably, the reference teaches that some positions

that are polymorphic in the human gene are not polymorphic in other non-primate animals, and vice versa (p.18950, Fig 1).

The converse line of reasoning demonstrates that just finding a identifying a MC4R gene in an animal other than a pig does not necessarily mean that a polymorphism in the gene will be predictive of meat quality or production traits (as is alleged by the specification). It is possible that an apparent MC4R homolog in a non-pig animal might not be functionally equivalent to the MC4R gene in pigs. Such a possibility is exemplified by Juppner (1995), which teaches that despite significant structural conservation, rat, opossum, and human PTH/PTHrP receptor homologs display distinct functional characteristics (Abstract; pp.39S-40S). Thus, even if homologs of the MC4R gene were identified and sequenced in other animals, and even if these new MC4R genes displayed polymorphisms, one would have to perform a large amount of experimentation to determine whether or not these putative polymorphisms would be indicative of any particular traits in the animals.

The amount of direction or guidance presented in the specification and the prior art of only one point mutation in the MC4R gene of one species of animal is minimal, given that just the redundancy of the genetic code of the approximately 350 amino acid protein would allow for several thousand different sequences when conserved or non-conserved mutations are considered, millions of different sequences for the pig MC4R gene may exist which may, or may not, have substantial functional differences or association with the traits of interest herein. There are no working examples of additional sequences other than those disclosed in either the specification or the prior art. Particularly, there is no disclosure of complex polymorphisms

including repeat link variance, insertions or deletions in MC4R ~~(as in claim 39)~~ which are also associated with favorable meat quality. In addition, a number of the claims recited that the instantly taught polymorphism, "or a polymorphism linked thereto" is used for the detection of favorable meat quality. However, the specification has not provided any evidence that polymorphisms linked to this single G→A change are in fact associated with meat quality traits. Such an association is highly unpredictable. There is no evidence in the specification provided that the identified polymorphism is causative of the observed traits. This is a significant absence of evidence, since it is possible that the polymorphism is merely a marker for the causative genotype. In light of the fact that the causative genotype has not been identified, it is unpredictable as to whether or not markers which are linked to the instantly disclosed polymorphism would be informative for the traits of interest herein (for example, as claimed in claims 30 and 31, for example).

The level of skill in the art of nucleic acid analysis is high (the Ph.D. degree with laboratory experience), the quantity of experimentation that would be necessary to determine even one additional polymorphism in the pig MC4R gene is substantial since there is no predictability for which sequences exist which code for polymorphisms in pig MC4R genes. Applicants have not disclosed how one would go about detecting polymorphisms associated with the traits of interest herein. Because there is no reason to expect that any additional polymorphism is associated with the production of meat with any favorable quality and because of the very large number of possible polymorphisms, screening for additional polymorphisms that would be indicators of these traits would require the rearing and subsequent slaughtering of many, many pigs in order to analyze their meat quality and in order to screen the MC4R gene for

informative polymorphisms. There is no evidence, however, of any frequency of significant polymorphisms. Further, even if polymorphisms were detected, the polymorphism may not correlate high meat quality. The instantly disclosed polymorphism may be coincident with and unrelated to a different, unlinked (on the chromosome) polymorphism such as another MC4R polymorphism or a polymorphism in an undetermined gene that actually determines meat quality. The instantly disclosed polymorphism would not have any meaning or effect, but might appear to influence meat traits due to it's close proximity to some other gene.

Furthermore, the level of unpredictability and the level of experimentation required to expand the instantly disclosed methods to include animals of other species are also quite high. There is no teaching in the specification that the disclosed polymorphism even exists in animals of other species. Since there is not evidence that the disclosed polymorphism is causative of the traits (as discussed above), it is highly unpredictable as to whether the polymorphism would mark the same traits in other animals that are slaughtered for meat. Further, in order to provide such evidence the skilled artisan would be required to undertake extensive studies of the meat quality of hundreds upon hundreds of different individual animals of each of many different species of animal. Such experimentation would be inventive in itself.

Due to the broad nature of the claims, the presence of only one working example, the extreme unpredictability of polymorphisms in the art, combined with the absence of teaching in the prior and the large quantity of experimentation necessary in the art support a conclusion that undue experimentation is required to make and use the invention as broadly claimed.

9. Claims 1, 4-10, 19-24, 29-37, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods comprising the analysis of nucleic acid sequences from animals wherein the nucleic acid sequences are associated with phenotypes or meat quality traits. The claims are thus broadly drawn to methods comprising the analysis nucleic acids that are indicative of these phenotypes and encompass the use of a multitude of different nucleic acid molecules of a wide variety of unique sequences.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis of a large number of nucleic acids comprising a wide variety of nucleic acid sequences. Each of the rejected claims encompasses at least one of the following: analyzing polymorphic sequences from any possible species of animal and/or analyzing porcine polymorphic regions other than the single disclosed point mutation at position 678 of instant SEQ ID NO: 1. Some claims require only that the detected polymorphism effect a TaqI restriction enzyme digestion pattern, such a polymorphism could be any insertion, deletion, or substitution of a sequence element to either create or destroy a TaqI site; thus the insertion of the recognition. Similarly, claim 20 requires only amplification of a sample with primers, the detection of a TaqI restriction pattern and comparison of the pattern to a second pattern that is associated with particular phenotypic traits. However, while amplification of the porcine MC4R sequence (thought the claim does not specify pig) taught by the specification

(resulting in instant SEQ ID NO: 1) creates a product with at least two TaqI sites (as evidenced by the formation of three restriction fragments), and the claims encompass the analysis of the entire MC4R gene, which is not disclosed for pigs or any other meat producing animal, and such a longer sequence could include additional TaqI sites. The rejected claims do not clearly define the nucleotide sequence information or structural limitations regarding what is considered a genotype or polymorphisms that is inherently associated with scrotal hernias. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the specification discloses a partial nucleic acid sequence a porcine MC4R gene (instant SEQ ID NO: 1). The specification also teaches an analysis of a single polymorphism in this gene, with the polymorphic site begin located at position 678 of SEQ ID NO: 1. The instant specification does not disclose any sequences from any animals other than pig, and does not provide any polymorphisms other than the aforementioned polymorphisms as associated with any particular meat characteristic or phenotype in general. The specification does not provide any other sequences encode "an amino acid position analogous to position 298 of human MC4R."

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other than nucleotide sequence or position within a particular gene), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, while the specification provides general information about methods to identify particular polymorphisms, and guidance

as to how to genotype an animal once a polymorphism has been identified and a correlation to a particular trait has been established, there is no guidance as to how one may *a priori* identify a genotype or polymorphism that is inherently associated with meat quality or other phenotypes.

In the instant application, the provided information regarding specific sequences and genotypes comprising particular polymorphisms used in the examples of the specification do not constitute an adequate written description of the broad subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the sequences, genotypes and polymorphic variants encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a statement that polymorphisms with a particular functionality or association are part of the invention and reference to a potential method for their identification. The particular nucleic acid sequences are themselves required.

In conclusion, the limited information provided regarding portions of the pig MC4R as provided in the examples of the instant specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for screening any animal for meat quality phenotypes or other general "phenotypes" using polymorphisms in the MC4R gene, or the TaqI restriction pattern of a PCR amplification.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

11. Claims 1, 4-10, 19, 30, 31, 33, 35, 36, 37, and 40 are rejected under 35 U.S.C. 102(a) as being anticipated by Rothschild *et al.* (WO 00/06777).

Rothschild *et al.* teach a method of identifying an animal which possesses a genotype indicative of a phenotypic trait which comprises obtaining a nucleic acid sample from said animal, assaying for the presence of a polymorphism in the MC4R gene of the sample said polymorphisms being one which has been previously shown to be significantly associated with a phenotypic trait, said polymorphism further being an aspartic acid codon which is changed to an asparagine codon at an amino acid analogous to amino acid 298 of the human MC4R gene, and associating said animal with said phenotypic trait based upon the genotype present in said animal. Further, Rothschild *et al.* teach a method for identifying a pig which possesses a genotype indicative of increased fat content, said method comprising obtaining a nucleic acid sample from said animal and assaying for the presence of a G → A polymorphism at position 678 of instant SEQ ID NO: 1 (the MC4R gene) (p. 4, lines 14-25). This polymorphism results in a change in the codon which encodes the amino acid at position the position in the pig MC4R gene anaglous to position 298 of the human gene, the polymorphism being either the aspartic acid codon or the asparagine codon. Rothschild et al. teach that animals homozygous for allele 1 had on average less back fat than those homozygous for allele 2 (p. 22). Instant claim 1 requires that the asparagine codon is "indicative of said animal more likely to have favorable meat

quality." In this case, the asparagine codon is indicitive of higher back fat versus aspartic acid. This is considered "favorable" meat quality as some people prefer fatty pork because it provides a more moist meat upon cooking. The useof the term "favorable meat quality" must be broadly interpreted in light of the prior art. Further, it is noted that the claim recites "meat quality characteristics such as marbling, color and drip loss" but the use of the term "such as" leaves the claim open to the inclusion of other possible meat quality traits. Rothschild *et al.* teach methods which employ allele specific oligonucleotides (see claim 7, for example), RFLP, PCR amplification and restriction analysis using Taq I (see claims 7-12, for example). Rothschild et al. teach amplificaiton with primers having instant SEQ ID NO: 5 and SEQ ID NO: 6 and that a polymorphism is found at position 678 (p. 10-11). Rothschild et al. teach using markers linked to the polymorphism such as S0331, BHT0433 and S0313 (see their clms 29-30, for example). The teachings of Rothschild *et al.* meet the limitations of all of the instant claims.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1, 4-10, 19, 20-24, 29, 32-37, and 40 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6803190.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the issued patent anticipate the instantly claimed invention. For example, claim 1 of the issued patent anticipates instant claims 1, 4, 20, 24, 29, 32, 33, 34, 36, and 40, claim 3 of the issued patent anticipates instant claim 5, claim 7 of the issued patent anticipates instant claim 6, claim 4 of the issued patent anticipates instant claim 7, claim 5 of the issued patent anticipates instant claim 8, claim 6 of the issued patent anticipates instant claim 9, claim 7 of the issued patent anticipates instant claim 10, claim 9 of the issued patent anticipates instant claim 19. Further, though the remaining claims are not clearly anticipated by the issued claims, the issued claims render obvious the claimed invention.

For example, regarding claims 21, 35, and 37, the issued patent does not include a step of selecting animals for breeding. However, it would have been prima facie obvious to have further selected the genotyped pigs for breeding based on the presence of the detected polymorphisms. One would have been motivated to do so in order to have provided a means for breeding pigs which have more consistent traits regarding back fat, daily gain, or feed intake.

Regarding claims 22 and 23, the method steps of amplifying and digesting nucleic acid sample are provided in the claims of the issued patent, the size of the restriction fragments would be an inherent property of the fragments amplified in the claims of the issued patent.

14. Claims 1, 4-10, 19, 30, 31, 33, 35, 36, 37, and 40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11, 20-23, and 28-32 of copending Application No. 10/834485. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application either anticipate or make obvious the instantly claimed invention.

Regarding instant claim 1, Claim 1 of the copending application teaches a methods which includes a step of identifying a polymorphism within the MC4R gene of a sample from an animal for the purpose of identifying an animal "which possesses a genotype indicative of the metabolic traits of fat content, growth rate, and feed consumption," with claim 2 reciting that the polymorphism is at position 678 or the PCR product of the MC4R gene. The polymorphism detected in the claims of the copending application is the same polymorphism being detected in the instant claims, and therefore the teachings of claim 2 of the copending application anticipate claim 1 of the instant application. Claim 3 if the copending application recites that the animal is a pig. Thus, it would have been prima facie obvious to one of ordinary skill in the art to have

performed the method of claim 2 of the copending application with a pig as the subject, and thus the invention of instant claim 4 is prima facie obvious in view of claims 1-3 of the copending application. The claims of the copending application also addressee method limitations such as those set forth in instant claims 5-10, namely in claims 7-11 of the copending application. Later claims teach that the polymorphism can be identified with the restriction enzyme Taq I and teach identifying restriction fragments which are the same size as those recited in instant claims, and also, the claims of the copending application teach methods for selecting animals with desired traits, methods for indirect selection, methods for identifying animals which include calculating the association between an MC4R genotype and a metabolic trait, and selecting animals. It would have been prima facie obvious to one of ordinary skill in the art to have modified the methods taught by the copending application so as to practiced any of them together, with the particular polymorphism disclosed in those claims for the detection of desired phenotypes as set forth in the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Remarks

Applicant's remarks are addressed in the order that they are provided, beginning on page 10 of the paper filed 4/1/02.

Regarding the new matter rejection, applicant states that the amendments of claims 33, 35, and 37 have overcome the rejection. However, neither the amendment nor the arguments address the broadened scope of the claims regarding "phenotypes" which is the subject of the

rejection. The rejection is applied in this continuation application to claims 33, 35, and 37. Additional rejections are set forth.

With regard to the 112 1st paragraph rejections, Applicant's arguments have been carefully considered but are not persuasive for the reasons that follow.

Applicants state on page 13 that the amended claims are drawn to identifying a specific polymorphism and specific meat traits in animals. However, this general characterization does not apply to all of the claims. For example, while claim 1 recites "favorable meat qualities" it uses the language "such as" to indicate that these meat qualities include "pH, marbling, color and drip loss" but it does not limit the detected traits to these traits. While independent claim 20 is limited with regard to the indicated phenotypic trait, the claim is not limited to the particular disclosed polymorphism from the instant specification because it is inclusive of the detection of any presence or absence of any TaqI site within the MC4R gene, since the claim requires isolating a sample comprising the seventh transmembrane domain, but not detecting a polymorphism within this domain. Independent claims 30, 32, 33, 35, 36, 37, and 40 are all also broad with respect to one or both aspects of these claims.

Applicant goes on to discuss the "relatively close evolutionary link" between pigs and other meat species. However, at the time the invention was made, the MC4R gene from "other meat species" was not isolated or sequenced, nor had anyone established the presence of any polymorphisms related to meat quality or other traits. There is no evidence on the record as to even what the sequence context in these undiscovered proteins would be for the MC4R gene, whether the gene is polymorphic in other "meat" species, or whether the polymorphisms have the same effect. An alignment which demonstrates a small structurally conserved region among

many animals is not evidence that an identical polymorphism exists in other species of animals or that such a polymorphism would have the same effect on other animals, as it is well known that the activity of a protein is dependent on its entire structure, and though there are conserved regions in these proteins that is not necessarily an indicator that the polymorphism or the associations of the polymorphism would be present in other species.

As a first point, it is noted that only three meat traits have been shown to be associated with alleles of a single disclosed polymorphism in a single species of animal and that for a fourth trait applicant was unable to show an association between alleles of the polymorphism and the trait. Furthermore, applicant has not demonstrated that the alleles of any particular other polymorphisms are closely enough linked to the instant polymorphism so as to be predictive of the same traits in pigs. Applicant has not shown any evidence that the instant polymorphism or any other relevant polymorphism exists in any other animals and is associated with any other phenotypic trait. Thus, applicant's assertions, which are merely attorney's arguments, are not persuasive. An alignment which demonstrates a small structurally conserved region among many animals is not evidence that an identical polymorphism exists in other species of animals or that such a polymorphism would have the same effect on other animals, as it is well known that the activity of a protein is dependent on its entire structure, and though there are conserved regions in these proteins that is not necessarily an indicator that the polymorphism or the associations of the polymorphism would be present in other species.

Applicant argues that failure to produce a significant association did not man the polymorphism was not indicative of favorable marbling. Applicant argues that for marbling, trend is in that direction and failure to reach significance may simply reflect the unequal genotype frequencies and the combination of lower mean values and high standards of error. Nonetheless, there is no persuasive evidence on the record which establishes a reliable predictive relationship in pigs or any other animal between alleles of the disclosed polymorphism or any other polymorphism and marbling. Such evidence is critical to an invention that purports to be able to predict an indication of favorable marbling in one allele compared to another. The importance of statistically significant results is discussed in the rejection.

Applicant states on page 15 "There are instances of conserved polymorphisms among species." Following are citations of a number of references from the post-filing date literature. These references were not provided for the examiner's review. Even if they were, references which are post-filing date can not be used to establish the state of the prior art at the time the invention was made. Further, these apparent specific examples of polymorphisms conserved among species do not establish that the polymorphism of the instant specification is conserved among species, nor that it is predictable which polymorphisms will be conserved among species and which will not. Further, it appears that the three references do not establish polymorphism in other species of animals, but identify polymorphism in one animal (pig, cow, or horse) and show that for all other organisms whose protein sequences for the particular protein were known, a single allele is present in the other species. There is no discussion in applicant's remarks that suggests that the same position was found to be polymorphic in other species.

On pages 15 and 16 applicant further discusses instances of gene conservation across species and conserved gene order across species. Again, the cited references were not provided, and many of them follow the filing date of the instant application. However, none of these references provide evidence to overcome the issues regarding these claims in particular, as set forth in the enablement rejection.

On pages 16 and 17 applicants repeat the argument that "Because of the evolutionary link between pigs and other meat-producing species" the findings of the instant specification can be applied to other animals. This is not persuasive for reasons already addressed.

Applicants argue that it would not be undue experimentation to identify other markers and polymorphisms around the MC4R gene. However, the entire coding sequence of the MC4R gene is not provided in the specification, nor is the genomic sequence "around the gene." There is no guidance as to the structure of these unidentified polymorphisms and such screening would require extensive unpredictable experimentation for pigs alone, let alone for providing this analysis for other or all "meat producing" species. Applicant argues that polymorphisms will be useful "at least out to a distance of 1 million" base pairs on either side of the gene, and in such a huge region polymorphisms can be found. This argument is attorney arguments which are not supported by evidence or written description on the record.

Applicant's refer to the declaration provided in the previous application. This declaration has not been entered into this application. If applicant desires consideration of this declaration in this application, it should be submitted. The declaration was discussed in detail in the final office action of the parent application.

Regarding the examiner's previous comments about the scope of the declaration versus the scope of the claims (i.e. that they are not commensurate) applicant states that the claims have been amended to the instantly disclosed polymorphism and particular traits. As previously discussed, this is not entirely accurate. Nonetheless, even if it were, the claims would still be broader in scope than the declaration which provides evidence only that the polymorphism is in the porcine population and the effects of the change on the porcine encoded polypeptide. Again, regardless of applicant's asserted expectation that the "different alleles disclosed will correlate with variability in this gene and in other meat producing animals" there is no evidence on the record that demonstrates this. The rejection provides extensive discussion as to why it would require undue experimentation to confirm applicant's assertions.

The rejection is applied in this newly filed continuation application.

Applicant traverses the 102 rejection under Rothschild et al. This rejection is applied to claims which are broad with regard to the phenotype that is indicated by the polymorphism. Applicant argues that there is no disclosure that the polymorphism is associated with pH, marbling, color and drip loss. The rejected claims are not so limited, as discussed in the rejection and throughout this office action. Applicant further argues that the marker for the four claimed meat quality measure is associated with allele 2. This argument is addressed in the rejection. Notably, since what is "favorable" is entirely a matter of perspective (i.e. some people prefer lean meat while some prefer the flavor added by fat), this argument is not persuasive to overcome the rejection. Further, not all of the rejected claims require that a particular allele is indicative of particular traits.

Conclusion

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as

general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Primary Examiner
Art Unit 1634

September 28, 2006